REMARKS

Change of Reference No.

Please note that the Attorney's Docket No. for this application has changed from 13054.01600 to 343054.01600. Thank you.

Withdrawal of Rejections and Objections

Applicants thank the Examiner for the reconsideration and withdrawal of the rejections and objections noted in the previous office action.

Claim Objections

The Examiner objects to claims 6, 14 and 16-18 for depending upon rejected base claims, but states they would be otherwise allowable. Applicants thank the Examiner for this indication, but believe that the following remarks demonstrate the allowability of the base claims at issue and therefore submit claims 6, 14 and 16-18 are allowable as written.

Claim Rejections 35 USC 112

The Examiner has rejected claims 12 and 19-52 under 35 USC § 112, first paragraph, as being containing subject matter not adequately described in the specification as filed.

First, the Examiner contends the term "double ortho ester," added to claim 12 in the previous response, is not supported in the specification. Applicants respectfully submit that the term is used in the specification at page 3, last full paragraph. However, the term is synonymous with diortho ester and the Examiner correctly points out that claim 12 does not limit claim 11. Thus, Applicants have amended claim 12 again to more closely correspond to the claim as originally filed. Claim 12 now refers to a diortho ester formed with a diketene acetal group. The claim as now amended avoids the use of the term "derivative" that was objected to in a previous action. Accordingly, Applicants request that the Examiner withdraw the objections to claim 12.

The Examiner also objected to claims 19-52, contending that ortho esters having the characteristic that hydrolysis directly detaches the hydrophobic portion from the hydrophilic portion are simply a subgenus of the ortho esters disclosed in the specification. The Examiner concludes that the claims therefore should be limited to that subgenus since there was no apparent support in the specification for such a limitation.

First, Applicants submit that all the ortho esters disclosed in the specification are characterized by a direct attachment to the hydrophobic portion through an oxygen atom. Applicants have amended independent claims 19, 30, 38, 42, 48 and 50 to clarify this feature. A direct consequence of the use of an oxygen atom to directly attach the hydrophobic portion is the result that hydrolysis of the ortho ester directly detaches the hydrophobic portion of the composition from the hydrophilic portion. Applicants hereby submit the Declaration of Dr. Jorge Heller to attest to these characteristics. Further, the Nantz reference does not share these features. Specifically, all the ortho esters disclosed by Nantz utilize a carbon atom to link the R1 group. The result of the Nantz chemistry is that hydrolysis leads to transesterfication of the ortho ester, which only subsequently may be cleaved to release the hydrophobic portion. The submitted Heller Declaration corroborates these observations.

For the above reasons, Applicants respectfully urge that the scope of the claims as amended is consistent with the disclosure in that all of the ortho esters disclosed in the specification share the oxygen atom linkage, and therefore, the characteristic direct detachment of the hydrophobic portion following hydrolysis. This is consistent with the arguments made to distinguish the Nantz reference in the previous response. Accordingly, Applicants request that the Examiner withdraw the §112 rejection of claims 19-52.

Claim Rejections 35 USC 102

The Examiner rejects claims 1, 2, 7, 10 and 15 as being anticipated by Klaveness et al. The Examiner states that Klaveness teaches polymers crosslinked by an ortho ester that comprise a hydrophilic portion and a hydrophobic portion. The Examiner concludes that the hydrolysis of the ortho ester would then release a hydrophobic portion from a hydrophilic portion. However, Applicants point out that the compositions disclosed by the Klaveness reference comprise a polymer of amphipathic molecules. The ortho ester bond functions to crosslink amphipathic molecules containing a hydrophilic group and a hydrophobic group to one another by a crosslinker. The crosslinker is positioned between two amphipathic molecules and if the crosslink is cleaved then two amphipathic molecules are regenerated. Klaveness does not describe a species wherein the hydrophilic portion is connected to a hydrophobic portion by a pH sensitive ortho ester so that when the ortho ester hydrolyzes the hydrophilic portion is separated from the hydrophobic portion. Applicants have amended independent claim 1 to clarify that the

claimed compositions are non-polymeric in nature, and thus distinguishable from the Klaveness disclosure. For these reasons, Applicants request that the Examiner withdraw the rejections of claims 1, 2, 7 , 10 and 15 under § 102 over Klaveness.

The Examiner has also rejected claims 1, 2, 5 and 15 as being anticipated by Harris. The Examiner states that Harris teaches compositions where PEG is conjugated to a phospholid and the PEG moieties are cross linked via an ortho ester. Accordingly, Harris suffers from the same deficiencies as Klaveness as discussed above. Namely, Harris discloses a polymer of amphipathic molecules wherein the ortho ester bond crosslinks the amphipathic molecules. The crosslinker is positioned between two amphipathic molecules and if the crosslink is cleaved then two amphipathic molecules are regenerated. Thus, Harris does not describe a species wherein the hydrophilic portion is connected to a hydrophobic portion by a pH sensitive ortho ester so that when the ortho ester hydrolyzes the hydrophilic portion is separated from the hydrophobic portion. As discussed above, Applicants have amended independent claim 1 to clarify that the claimed compositions are non-polymeric in nature, and thus distinguishable from the Harris disclosure. For these reasons, Applicants request that the Examiner withdraw the rejections of claims 1, 2, 5 and 15 under § 102 over Harris.

Claim Rejections 35 USC 103

The Examiner has rejected claims 1, 2, 11-13, 19, 30-33, 38 and 39 as being obvious over Sparer in view of Mohr. The Examiner states that Sparer discloses bioerodable poly(ortho esters) and beneficial agents, and specifically notes that a beneficial agent such as coenzyme Q (disclosed by Mohr) may be linked by an ortho ester to a polyethylene glycol.

With respect to claim 1 and its dependents, Applicants have amended the claim to clarify that the claimed composition is non-polymeric in nature. In contrast, Sparer discloses only polymeric compositions and the Mohr does not complete the reference. Accordingly, Applicants request that the Examiner withdraw the §103 rejection of claims 1, 2 and 11-13.

Applicants respectfully point out that in the previous response, independent claims 19, 30 and 38, were limited to require an "encapsulator selected from the group consisting of lipsomes, emulsions, micelles and lipidic bodies." As the Examiner recognizes, Sparer discloses a polymeric implant. Sparer does not suggest any of the specific encapsulators required by the claims. Further, Mohr does not compensate for this deficiency.

For these reasons, Sparer and Mohr do not suggest lipsomes, emulsions, micelles and lipidic bodies and thus, Applicants request that the Examiner withdraw the §103 rejection of claims 19, 30-33, 38 and 39.

Additionally, citing Mohr for the proposition that coenzyme Q is a beneficial agent is not supported by current scientific research. The claim that ubiquinone is a beneficial agent is not support by a variety of human clinical trials, in spite of the observation by Mohr that dietary administration of coenzyme Q leads to higher plasma levels in plasma and lipoproteins, therby increasing resistance of LDL to radical oxidation. The beneficial value of dietary supplmentation of coenzyme Q has not been substantiated in many carefully controlled clinical trials. For instance, Lesperance et al., (Breast Cancer Res treat 76:137-143, 2002) administered mega-dose vitamins including coenzyme to breast cancer patients and conclude "breast-cancer-specific survival and disease-free survival times were not improved for the vitamin/mineral treated group over those for the controls". Similarly Prince et al., (Aliment Pharmacol. Ther. 17:137-143, 2003) conclude "although oral antioxidant supplementation appears to be safe, we could not find any evidence for a benefical effect on fatigue or other liver related symptoms". The December 2002 Harvard Heart Letter undertook "A close look at coenzyme Q and policosanol." They conclude Coenyzme Q "appears safe but that there's no good evidence that it improves heart health." Ellis & Scott, in the highly respected medical journal Lancet 361:1134-1135, 2003, state in the context of myocardial disease "By contrast supplementation with commercially available Q10 has no robust evidence of clinical benefit. With supplementation, serum concentrations are raised, although we could find no good data to suggest a clinically important rise in coenzyme Q within muscle mitochondria, where coenzyme Q's activity is reported to be the major cause of concern."

Thus, the suggestion that coenzyme Q is a benefical compound as classified by Sparer is not supported by the current medical literature. The suggestion that the resulting composition formed by the conjugation of PEG to Coenzyme Q via an ortho ester would provide a controlled-release dosage of ubiquinone for a benefical effect is not supported by the literature. In fact, ubiquinone and coenzyme Q are hydrophobic compounds, simply injecting coenzyme Q would provide a controlled release depot of this compound; attaching a PEG group would make the compound more water soluble and cause it to be eliminated from the site of injection much more rapidly than the non-modified coenzyme Q. Thus there would be no medical reason for doing so.

For these reasons, Sparer and Mohr do not suggest the combination cited by the Examiner. Thus, Applicants request that the Examiner withdraw the §103 rejection of claims 19, 30-33, 38 and 39.

Conclusion

Based on the above remarks and amendments, Applicants submit that the pending claims are patentable and request their early allowance. To expedite prosecution, the Examiner may contact the Applicants representative Nathan Koenig at (541) 806-2252.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Mail Stop AF, P.O. Box 1450, Alexandria, VA 22313-1450, on July 14, 2003, 2002.

Dated: July 14, 2003 By: _____
Rebecca M. Klits